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Letter to the Editor

Reply to the letter to the editor "before attributing impaired cognition in the elderly to COVID-19, all influencing factors must be considered"

We thank Finsterer J. for the comments on our paper entitled "SARS-CoV-2 infection and cognition in community-dwelling and nursing home residents in southern Switzerland", published in *Brain, Behavior, & Immunity - Health*.

First, we agree that RT-PCR is the gold standard diagnostic test to evaluate ongoing acute SARS-CoV-2 infection and COVID-19 (Sidiq et al., 2020). However, our focus was infection regardless of symptoms and their severity. RT-PCR has limitations. False negatives may occur using RT-PCR tests if the sample is not collected correctly and the viral load is low (Sidiq et al., 2020). Blood-based serology of circulating antibodies is the optimal choice, specific and sensitive, to identify past virus exposure, which was the focus of our study (Kilic et al., 2020). In addition, asymptomatic individuals, in particular older adults who were the target population of our study, may be reluctant to undergo RT-PCR test (Morales et al., 2021). We agree that the cross-sectional design of our study limits causal inferences in the infection to cognitive impairment association.

Second, we agree that vaccination status is a critical factor to consider in Long Covid studies and we confirm that vaccination was not an exclusion criteria to participate in our study. Our essay allowed to distinguish between infection- and vaccine-induced immune responses. We measured antibodies targeting nucleocapsid (N) proteins of the virus (developed only after infection) and antibodies targeting the Spike (S) protein. With anti-N and anti-S antibodies we could distinguish between cases (i.e., infected only) and controls (non-infected irrespective of vaccination status). The grouping procedure was previously reported in Amati et al. (2023), and cited in our paper. Evidence on the potential confounding effect of vaccination in the association of SARS-CoV-2 with cognitive functioning was extremely patchy and weak when we conducted our study and chose our statistical models (Gao et al., 2022).

Third, that we did not have information and data on drug intake and comorbid conditions was an already acknowledged limitation of our study, which we share with previous studies (Almeria et al., 2020). Future studies should consider whether and the extent to which poor health may mediate or confound the association between SARS-CoV-2 infection and cognition.

Finally, while collecting data through proxies of participants may reduce the accuracy and reliability of measures, this is commonly done in frail individuals including institutionalized older adults (Griffiths et al., 2020; Hladek et al., 2021). Nurses are optimal proxies because they are knowledgeable in health conditions and cognition and may also combine their close and constant observations with medical records to which they have access to provide care. We used Standardized Operational Procedures (SOPs) to assist nurses in data collection. Errors in filling in the questionnaires were likely minimal, unsystematic, and non-differential between cases and controls. Finally, we focused on cognition. Brain structure and function measures were beyond the scope of our study.

CRediT authorship contribution statement

Greta Rizzi: Writing – original draft. **Emiliano Albanese:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

There are no conflict of interest among authors.

Data availability

No data was used for the research described in the article.

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Greta Rizzi
Institute of Public Health, Faculty of Biomedical Sciences, Università della Svizzera italiana, Switzerland

Emiliano Albanese[*]
Institute of Public Health, Faculty of Biomedical Sciences, Università della Svizzera italiana, Switzerland

[*] Corresponding author.
E-mail address: emiliano.albanese@usi.ch (E. Albanese).